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Amino Acids in Health and Disease: New Perspectives

Editor
Seymour Kaufman

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Amino Acids in Health and Disease: New Perspectives

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Preface

This book is based on the UCLA Symposium "Amino Acids in Health and Disease: New Perspectives", that was held at Keystone, Colorado, May 30–June 4, 1986.

As is evident even from the most cursory glance at the Table of Contents, the goal of the symposium was not to provide a general picture of the status of knowledge of all of the amino acids. Rather, there was a heavy, albeit not exclusive, emphasis on the aromatic amino acids, specifically, phenylalanine, tyrosine and tryptophan.

One of the reasons for this emphasis is that this group of amino acids, perhaps more than any other, provided some of the earliest evidence for what has become one of the dominant themes in the field of amino acid biochemistry and physiology. In addition to the established role that amino acids play as building blocks of proteins, many of them play essential regulatory roles in organisms.

The aromatic amino acids play these other roles indirectly, by serving as precursors of the monoamine neurotransmitters, dopamine norepinephrine and serotonin and, in the case of tyrosine, as precursor of the hormone thyroxine. A major part of the symposium dealt with newer aspects of the conversion of the aromatic amino acids to monoamine neurotransmitters, as well as with the function of the neurotransmitters themselves.

The cerebral metabolism of the aromatic amino acids and of the other large neutral amino acids is known to be regulated at the level of transport of these amino acids across the blood-brain barrier. The hallmark of this system is that the individual amino acids of this group compete with each other for entry into the brain. Because of its importance to our understanding of amino acid metabolism, the symposium started with a session on amino acid transport into the brain, as well as transport in the renal tubule.

Following this session, various aspects of the regulation in brain of the synthesis of monoamine neurotransmitters, including regulation by availability of the amino acid precursors, were discussed.

Because the conversion of the aromatic amino acids to monoamine neurotransmitters involves the hydroxylation of the precursor amino acids, the pterin-dependent aromatic amino acid hydroxylases occupy a central position in the regulation of the synthesis of this class of neurotransmitters. The en-

zymology and the molecular biology of these hydroxylases were covered in the next session.

Amino acids and monoamine transmitters are involved in the control and modulation of a wide variety of physiological and behavioral responses. Several sessions were devoted to two different types of behavior and physiological control, appetite, and blood pressure.

The genetic disease, phenylketonuria, results in profound disturbances in the metabolism of phenylalanine, as well as less marked but still crucial changes in the metabolism of tyrosine and tryptophan. Because of the unique lessons that this disease can teach us about the metabolism of the aromatic amino acids, the last session was devoted to the biochemistry, molecular genetics, and therapy of phenylketonuria and its variants.

We gratefully acknowledge G.D. Searle and Company for its generous sponsorship of this conference. We also wish to thank the participants, the session chairmen, those who helped to organize the program, especially Drs. J. Fernstrom, J. Filer, R. Roth, L. Stegink, and S. Woo, and finally the members of the staff of the UCLA Symposia on Molecular and Cellular Biology, in particular, Robin Yeaton and Betty Handy.

Seymour Kaufman

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ROLE OF MEMBRANE TRANSPORT IN INTERORGAN AMINO ACID FLOWS: WHERE DO THE DEPLETED AMINO ACIDS GO IN PHENYLKETONURIA?[1]

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ABSTRACT Membrane transport processes are among the factors determining the direction and intensity of interorgan amino acid flows. Competition by excess phenylalanine with important flows to the brain across the blood-brain barrier has long been attributed a place in retardation of the infant brain in PKU. Concurrent declines in the plasma levels of a somewhat different set of amino acids have, however, remained a paradox. My laboratory has shown that an amino acid in excess may occasion sequestering of certain other amino acids by inhibiting the transport route of their exodus from, more than that for their entry into, such tissues as liver and muscle, at the same time that it inhibits the inward movement of certain other amino acids across the blood-brain barrier. The total effect of these two actions I propose determines which amino acids may be depleted in the brain in the hyperphenylalaninemia of PKU, or in the leucine accumulation of maple syrup urine disease.

The tissues of our bodies are nourished not simply by a tide of amino acids, sugars, and other nutrients flowing directly to each cell from their alimentary source, as an oversimplified global view of nutrition might suppose. Instead, virtually every cell in the organism is nourished also to an important extent by fluxes of nutrient molecules arising

[1]This work was supported by Grants AM 32281 and AM 25548 from the National Institutes of Health, United States Public Health Service.

from various other cells. These flows are given their direction and volume, as one important factor by complex competitions among the rates of chemical reactions that on the one hand generate and on the other hand utilize the concerned molecules in various tissues. But as a second important factor the direction and size of these flows are influenced by asymmetries contributed by the transport processes into which they enter in their obligated passage of the two or more cellular membranes separating the source and the target of each flow. The study of membrane transport seeks at this stage of research to interpret the comparative roles of these factors in determining interorgan flows (1,2).

Specifically for the amino acids, a degree of neglect of the contribution of interorgan nutrition has created an overly sharp division between the amino acids that must be provided in the diet and those that under suitable circumstances may be dispensable as dietary constituents. We rarely neglect the importance of the interorgan flows of the equally dispensable glucose, but we may be tempted to underemphasize those for example of the supposedly dispensable alanine or glutamine. Just because an amino acid can be synthesized in the organism, perhaps in the very cell we may be considering, does not mean that this cell necessarily maintains a concentration sufficient to sustain its normal utilization there. Instead its sequestering in another cell by an aberrance in membrane transport may, as we will consider here, lead to a local wasteful rate of utilization that leaves some other tissue deprived. The role of transport in the economy of a nutrient is more obvious when the "dispensable" nutrient arises outside the cell under discussion; but the central question is nevertheless the same (2): For a given nutrient, is a physiologically sufficient level in, or flow of a given nutrient to, a given cellular compartment maintained?

I offer an example from the recent literature: Occasionally infants need to be sustained at minimal protein intakes to minimize intoxication from a congenitally incomplete catabolism, for example of the branched-chain amino acids. This nutritional therapy is managed by adding selected amino acids to the dietary formula, avoiding any that contribute toxicity, to an amount of milk that does not exceed the amounts tolerated of any poorly metabolized amino acids. It was observed by Nyhan and his associates that acceptable growth could be obtained (Table I) at a much lowered protein intake if a supplement of the "dispensable" amino acid, alanine, is supplied in such a restricted diet, an effect not mimicked by glycine, glutamate, or a mixture of dispensable amino acids. Does